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Prostate capsule sparing versus nerve sparing radical cystectomy for bladder cancer: Results from a randomized controlled trial

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Abstract

Purpose—Prostate capsule sparing and nerve sparing cystectomies are alternative procedures for bladder cancer that may reduce morbidity while achieving cancer control. However, the comparative effectiveness of these approaches has not been established. We sought to evaluate the functional and oncologic outcomes of patients undergoing these two procedures.

Material and Methods—We performed a single-institution trial of bladder cancer patients who had a negative transurethral prostatic urethral biopsy and negative transrectal prostate biopsy. Men were randomized to prostate capsule sparing or nerve sparing cystectomy with neobladder creation. Patients were stratified by Sexual Health Inventory for Men (SHIM) scores (SHIM >21 or ≤21). Our primary endpoint was 12-month overall urinary function as measured by the bladder cancer index (BCI). Secondary endpoints included sexual function, cancer control, and complications.

Results—Forty patients were enrolled in the study, with 20 patients in each arm. Urinary function at 12 months decreased by 13 and 28 points in the prostate capsule sparing and nerve sparing groups, respectively (p=0.10). Sexual function followed a similar pattern (p=0.06). There

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were no differences in recurrence-free, metastasis-free, or overall survival (all $p>0.05$). The rate of incidentally detected prostate cancer was similar ($p=0.15$).

Conclusions—Our study provides a randomized comparison of prostate capsule sparing and nerve sparing cystectomy techniques. We found no differences in functional or oncologic outcomes between the two approaches, although our study was underpowered due to lack of patient accrual.

Keywords

bladder cancer; cystectomy; prostate-capsule sparing; nerve sparing; randomized clinical trial

INTRODUCTION

Radical cystectomy is the standard treatment for patients with either localized muscle-invasive cancer or non-muscle-invasive urothelial cancer refractory to intravesical therapy,¹ yet is associated with significant morbidity.² In an effort to reduce morbidity, both prostate capsule sparing and nerve sparing cystectomy have been described in case series as potential ways to decrease side effects and improve quality-of-life outcomes without jeopardizing oncologic control. These approaches attempt to preserve the neurovascular bundles lateral to the prostate. In addition, the prostate capsule sparing technique avoids extensive dissection of the pelvic floor musculature and the external urethral sphincter. Both these approaches may result in improved erectile and urinary function.³⁻⁹

The benefits of these two approaches, however, compared with the more traditional radical cystectomy technique **are largely demonstrated in retrospective studies**. Limited evidence **from randomized trials** is available on the relative effectiveness of the prostate capsule sparing and nerve sparing approaches in terms of functional outcomes. Further, and perhaps more importantly, the relative cancer control of these two approaches is unknown. Despite the appeal of prostate capsule sparing radical cystectomy, there are concerns that leaving behind part of the prostate may lead to higher rates of positive surgical margins and residual or future prostate cancers.¹⁰ Even if voiding and sexual function are improved for these patients, the prostate capsule sparing approach would ultimately be detrimental in such cases.

For these reasons, we performed a phase II randomized clinical trial evaluating the functional and oncologic outcomes of patients undergoing either a prostate capsule sparing or nerve sparing radical cystectomy with neobladder creation. Understanding potential differences in voiding function, sexual function, and cancer control between these two patient populations will determine the potential of these approaches as alternative extirpative techniques for bladder cancer.

METHODS

Study design

We conducted a single-institution, clinical trial in which patients with urothelial cancer were randomized to prostate capsule sparing or nerve sparing cystectomy (NCT01824329). The

study protocol was approved by our institutional review board. Patients provided written informed consent. **Five surgeons participated in this study.** Enrollment began in August 2007, and was completed in October 2011. Follow up was completed in January 2013.

Patient population

Eligible patients included men 18 years or older with clinical stage T2 urothelial cancer diagnosed within 3 months of enrollment.¹¹ Patients downstaged after receiving neoadjuvant chemotherapy (e.g., from stage cT3 to cT2) were eligible. Concern for nodal or metastatic disease on pre-operative imaging excluded patients from participation. Specific imaging, laboratory, and follow-up requirements are displayed in the appendix. All men underwent a transurethral biopsy of the prostatic urethra and a 12-core transrectal ultrasound-guided prostate biopsy.¹² The transurethral biopsy was performed with a resectoscope and tissue was sampled from the 5 o'clock and 7 o'clock positions; the transrectal prostate biopsy targeted all areas of the prostate as much as was feasible through the transrectal approach, including the anterior apex. Additional exclusion criteria included a creatinine level > 2.2 mg/dL, prior pelvic radiation to the bladder or prostate, or a history of a radical prostatectomy.

Among those who consented to randomization, 5 patients were excluded due to prostate cancer on biopsy, 2 patients withdrew their consent, and 1 patient was excluded due to surgeon judgment.

Study intervention

Patients were randomly assigned to receive either a prostate capsule sparing or nerve sparing radical cystectomy with neobladder urinary diversion. Randomization occurred the morning of surgery and patients were informed of their assignment as part of informed consent. Both of these procedures share many common steps; the main difference is how the prostate is managed.¹³ With the prostate capsule sparing approach, a supra-ampullar dissection was performed to develop a plane anterior to the seminal vesicles. The endopelvic fascia was preserved on either side of the prostate. The prostate capsule was incised with a transverse incision on the distal anterior surface of the prostate and the adenoma was dissected from the capsule. For the nerve sparing approach, the entire prostate and seminal vesicles were removed along with the bladder. The neurovascular bundles were spared by performing an intrafascial dissection in a retrograde fashion.

These different cystectomy techniques necessitated different approaches to the urethral anastomosis. With the prostate capsule sparing approach, the neobladder was anastomosed to the capsule of the prostate, whereas with the nerve sparing approach, the neobladder was anastomosed to the urethral stump.¹³ In both approaches, an extended pelvic lymph node dissection was performed, including dissection around the common iliac arteries.

Study measures

Men were stratified based on their Sexual Health Inventory for Men (SHIM) questionnaire, a 5-question validated questionnaire used to evaluate sexual function. The SHIM provides a score of 5 to 25 with a score of ≥ 21 indicating erectile dysfunction with a sensitivity of 98%

and a specificity of 88%.¹⁴ Accordingly, stratification was based on a SHIM score of > 21 or 21.

Baseline assessments included patient demographics, tumor characteristics, and urinary and sexual function as measured by the bladder cancer index (BCI). The BCI is a validated bladder-cancer specific health-related quality-of-life instrument that measures urinary, sexual, and bowel function and bother domains.¹⁵ The index consists of 34 items within 3 primary domains (urinary, bowel, sexual) and 2 subdomains (function, bother).¹⁵ Item responses are based on Likert scales, with scores standardized to a 0-100 point scale in which higher scores correspond to better health states. Each domain has been validated independently.¹⁵

Peri-operative characteristics examined included estimated blood loss and operative time. Clinical outcomes measured included hospital length of stay, 30-day readmission rates, and 90-day major complication rates. A major complication was defined as Common Terminology Criteria for Adverse Events (CTCAE) grade 3 (i.e., severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living) or higher.¹⁶

Study outcomes

The primary endpoint was 12-month overall urinary function compared with baseline. Secondary endpoints included 12-month overall sexual function compared with baseline, oncologic outcomes, as measured by margin status, time to disease recurrence, and overall survival at 24 months, peri-operative outcomes, and complications. An independent data and safety monitoring committee met every 3 months to review the study conduct, adverse events, and the validity and integrity of the data.

Statistical analysis

The randomized selection design¹⁷ was used to assess urinary function in prostate capsule sparing and nerve sparing cystectomy patients. Patients were randomized using a balanced stratified (SHIM > 21 vs. SHIM ≤ 21) randomized block design to the surgical treatment arms. With 41 subjects per surgical group, there was a 90% probability of selecting the superior treatment, assuming that the superior treatment had a 7-point improvement in 12-month urinary function change from baseline compared with the inferior treatment. The analyses were based on an intent-to-treat approach.

Characteristics between groups were compared using the Student's t-test for continuous variables and chi-square tests for categorical variables. Urinary and sexual functions were evaluated using the Wilcoxon Rank test. Parameters relating to clinical and pathologic stage were assessed using the Jonckheere-Terpstra test. Recurrence-free, metastatic-free, and overall survival were analyzed using Kaplan-Meier methods and tested using the log-rank test. All analyses were performed using SAS, version 9.2 (SAS Institute, Cary, NC). The probability of a type I error was set at 0.05, and all testing was 2-sided.

RESULTS

Forty patients were enrolled in the study with 20 patients randomized to each cohort. Baseline patient characteristics were similar between groups (Table 1). In both groups, the operation was most commonly performed via an open approach. For robotic procedures, the neobladder was created extracorporeally. A Hautmann reservoir was created in > 90% of patients.

The 12-month BCI was completed by 36 (90%) of the 40 enrolled patients; the primary endpoint (urinary function) was evaluated in 34 (85%); 2 patients were not evaluated for urinary function and 4 patients were not evaluated for sexual function due to missing data from sections of the BCI. For urinary function, there was no statistical difference between the two approaches ($p=0.10$). Average urinary function at 12 months compared with baseline levels decreased by 13 points (standard deviation [SD]=30) and 28 points (SD=33) for prostate capsule sparing and nerve sparing patients, respectively (Table 2). A waterfall plot demonstrating the change in urinary function for the study population is shown in Figure 1. Average sexual function at 12 months compared with baseline decreased by 1 point (SD=11) and 23 points (SD=30) for the prostate capsule sparing and nerve sparing patients, respectively ($p=0.06$). A waterfall plot demonstrating changes in sexual function stratified by SHIM score is shown in Figure 2.

In examining responses to specific urinary and sexual function questions, both groups experienced the slowest improvement in nighttime frequency and leakage; the nerve sparing group also had slower improvement in daytime frequency. Twenty-two and 17% of prostate capsule sparing and nerve sparing patients performed intermittent catheterization and 55% and 65% of prostate capsule sparing and nerve sparing patients used aids or medications for erectile function, respectively.

The pathologic outcomes were similar between the two groups (Table 2). The majority of patients had tumor stage T2 and had node-negative disease. Of the seven node-positive patients, 3 had received neoadjuvant chemotherapy. Prostate cancer was detected in 3 patients in the prostate capsule sparing cohort and 8 patients in the nerve sparing cohort. There were no differences between the groups in terms of recurrence-free, metastasis-free, and overall survival (Figure 3).

Of the 40 patients with negative biopsies who underwent surgery, 11 (28%) had prostate cancer detected on final pathology (Table 3). Seven (88%) of the 8 nerve sparing patients with prostate cancer had an undetectable PSA; the 3 prostate capsule sparing patients with prostate cancer had PSA's of <0.1, 0.1, 0.2; none of these patients received additional treatment. Gleason scores and pathological prostate cancer stages were similar between the 2 groups (both $p>0.05$). One patient had a positive prostate cancer margin but had an undetectable prostate-specific antigen (PSA) at follow up.

The peri-operative characteristics and clinical outcomes between the cohorts were similar (Table 4). Operative times were 395 and 411 minutes for the prostate capsule sparing and nerve sparing approaches, respectively ($p=0.65$). No differences were observed in 30-day readmission rates or 90-day major complication rates (both $p>0.05$).

DISCUSSION

Our study provides a randomized comparison of prostate capsule sparing and nerve sparing cystectomy techniques. We found no differences in functional or oncologic outcomes between the two approaches, although our study was underpowered due to lack of patient accrual. The two approaches had similar peri-operative outcomes and complication rates.

Interest in prostate capsule sparing cystectomy stems from its potential to reduce morbidity. The approach preserves the neurovascular bundles, spares the seminal vesicles, and limits the dissection of the pelvic floor musculature around the external sphincter, which are all techniques thought to improve voiding and erectile function compared with the nerve sparing approach or traditional cystectomy.¹³ Indeed, over three-fourths of patients report preserved erectile function with the prostate capsule sparing approach.^{3, 18, 19} Moreover, the vast majority of patients report both daytime and nighttime urinary continence.^{3, 6, 18, 20, 21}

Our **findings showed** that the prostate capsule approach had **similar** functional outcomes compared with the nerve sparing approach. **Although** the size of the observed effect was greater than what we defined as clinically important for both urinary and sexual function, the variability of the effect required the sample size to be larger than what we were able to accrue during the study period. Patients undergoing the prostate capsule sparing approach reported urinary and sexual function that was substantially closer to baseline than those undergoing the nerve sparing approach at 12 months (Table 2, Figures 1 & 2). **It is unclear whether or not** statistically significant differences in urinary and sexual function between the two approaches may have emerged had we reached our targeted recruitment of 82 patients (essentially doubling our sample size).

Nevertheless, findings from our study improve our understanding of urinary and erectile function outcomes following the prostate capsule sparing and nerve sparing approaches, as well as the oncologic implications of these two approaches. There is appropriate concern that the prostate capsule sparing approach may jeopardize both bladder and prostate cancer control.¹⁰ Prostate cancer is incidentally detected in about 40% of radical cystectomy specimens, of which approximately 20% are clinically significant.^{10, 22} Further, about 25% of incidentally detected prostate cancers involve the prostatic apex,²² which may hinder complete resection with the prostate capsule sparing approach. In addition, the prostate harbors urothelial cancer in as many as half of cystectomy specimens, which further raises concerns about cancer control in the prostate capsule sparing setting.²²⁻²⁴

Our oncologic findings reinforce these concerns. Despite strict eligibility criteria (e.g., a negative transurethral and prostate biopsy), 15% and 40% of prostate capsule sparing and nerve sparing cystectomies, respectively, **still** had prostate cancer **on final pathology**.

Although there were no differences in recurrence-free, metastatic-free, or overall survival at this early surveillance point, the high incidence of prostate cancer gives pause for concern. **Fortunately**, the majority of these patients had low-risk disease. While the biopsy did not detect prostate cancer in these patients, newer technologies (e.g., prostate magnetic resonance imaging, prostate cancer antigen 3 [PCA3] test) may help better identify them in the future.

In interpreting our results, it is important to consider several limitations. First, we were unable to meet our targeted accrual. Historically, it has been challenging to compare competing procedures in a randomized trial in the United States.²⁵ Patients tend to be skeptical of surgical clinical trials due to the invasiveness and irreversibility of surgery.²⁶ Further, patients generally have a low willingness to participate in surgical trials due to an aversion to randomization and a desire to select the intervention.²⁷ Recruitment rates in surgical randomized clinical trials are typically less than half of all eligible patients.²⁸ Within urology, the Surgical Prostatectomy versus Interstitial Radiation Intervention Trial (SPIRIT) (NCT00023686) is an example of a randomized trial of competing procedures that closed prematurely, having accrued only 56 of the intended 1,980 patients.^{25, 29} Nonetheless, valuable information can still be obtained from a trial that does not meet accrual.

Second, this was a single-institution study. Designing a multi-institutional study, and thus, drawing from a larger pool of patients may have helped patient recruitment. Third, performing a prostate capsule sparing cystectomy is likely associated with a learning curve for the surgeon. Developing a plane between the seminal vesicles and base of the bladder is challenging. Nonetheless, the surgeons who participated in this study were all fellowship trained in oncology and had significant experience performing cystectomies.

These limitations notwithstanding, there are two important findings in this study that merit consideration. First, although our study **did not meet accrual**, it provides initial estimates that suggest that the prostate capsule sparing approach **has similar** functional outcomes **as** the nerve sparing approach. Second, in highly selected individuals (e.g., negative prostatic urethral and transrectal prostate biopsies), the prostate capsule sparing and **nerve sparing** approaches **had** similar, **albeit high, rates of cancer detection**. In elucidating both the functional and oncologic issues, a future multi-institutional study may help overcome the accrual barrier and further inform the debate surrounding the utility of the prostate capsule sparing approach.

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Figure 1. Change in urinary function for patients randomized to prostate capsule sparing and nerve sparing cystectomy

Average urinary function at 12 months compared with baseline decreased by 13 ± 30 points for prostate capsule sparing patients and decreased by 28 ± 33 points for nerve sparing patients. There was no difference in urinary function between the two approaches ($p=0.10$). P value generated from Wilcoxon Rank test.

Figure 2. Change in sexual function stratified by SHIM score for patients randomized to prostate capsule sparing and nerve sparing cystectomy

In the nerve sparing cohort, 10 patients had a SHIM ≤ 21 and 10 patients had a SHIM > 21. In the prostate capsule sparing cohort, 11 patients had a SHIM ≤ 21 and 9 patients had a SHIM > 21. Average sexual function at 12 months compared with baseline decreased by 1 ± 11 points for prostate capsule sparing patients and decreased by 23 ± 30 points for nerve sparing patients. There was no difference in sexual function between the two approaches ($p=0.06$). P value generated from Wilcoxon Rank test.

Figure 3. Recurrence-free (A), metastatic-free (B), and survival (C) probability in patients randomized to prostate capsule sparing and nerve sparing cystectomy

Prostate capsule sparing and nerve sparing patients demonstrated no differences in recurrence-free, metastatic-free, or survival probability (all $p > 0.05$). P value generated by the log-rank test.

Table 1

Demographics and clinical characteristics of the study population

Characteristics	Prostate capsule sparing cystectomy (n=20)	Nerve sparing cystectomy (n=20)	P Value
Age (years), mean (SD)	58 (10)	59 (6)	0.70
ECOG performance status (%)			0.49
0	20 (100)	18 (90)	
1	0 (0)	2 (10)	
Body mass index, mean (SD)	30 (5)	31 (4)	0.76
Neo-adjuvant chemotherapy (%)	8 (40)	10 (50)	0.75
Clinical stage (%)			0.23
Ta/Tis	3 (15)	2(10)	
T1	7 (35)	4 (20)	
T2/T3	10 (50)	14 (70)	
Approach (%)			0.73
Open	15 (75)	13 (65)	
Robotic-assisted	5 (25)	7 (35)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group

* P value generated from Jonckheere-Terpstra test; other p values generated from Student's t-test for continuous variables and the Fischer's exact test or Mantel-Haenszel chi-square test for categorical variables.

Table 2

Pathologic outcomes of the study population

Characteristics	Prostate capsule sparing cystectomy (n=20)	Nerve sparing cystectomy (n=20)	P Value
Median follow-up time (months)	41	37	0.75
Pathologic tumor stage (%)			0.45 [*]
T0	8 (40)	8 (40)	
Ta/Tis	6 (30)	2 (10)	
T1	3 (15)	4 (20)	
T2	1 (5)	2 (10)	
T3	2 (10)	4 (20)	
Pathologic nodal stage (%)			0.19 [*]
N0	18 (90)	15 (75)	
N1	1 (5)	1 (5)	
N2	1 (5)	4 (20)	
Positive surgical margins (%)			
Soft tissue	0 (0)	0 (0)	0.99
Ureter	1 (5)	1 (5)	0.99
Urethra	0 (0)	0 (0)	0.99
Cancer present in urethra (%)	2 (10)	4(20)	0.66
Prostate cancer (%)	3 (15)	8 (40)	0.15
Number of lymph nodes removed, mean (SD)	16 (10)	16 (8)	0.91

* P value generated from Jonckheere-Terpstra test; other P values generated from Student's t-test for continuous variables and the Fischer's exact test or Mantel-Haenszel chi-square test for categorical variables.

Table 3

Prostate characteristics in the study population

Characteristics	Prostate capsule sparing cystectomy (n=20)	Nerve sparing cystectomy (n=20)	P Value
Pre-operative/biopsy characteristics			
Pre-operative PSA (ng/mL), median (minimum, maximum)	1.9 (0.2, 5.5)	1.0 (0.3, 5.1)	0.07
Prostate volume (mL) by ultrasound, mean (SD)	33 (14)	26 (8)	0.96
Prostate biopsy results (%)			0.99
Negative	18 (90)	17 (85)	
HGPIN	2 (10)	3 (15)	
Post-operative/pathology characteristics			
Prostate cancer (%)	3 (15)	8 (40)	0.15
Gleason score (%)			0.10 [*]
6	2 (67)	8 (100)	
7	1 (33)	0 (0)	
Pathologic tumor stage (%) ^{**}			0.45 [*]
T2a	2 (67)	7 (88)	
T2b	1 (33)	1 (12)	
Positive margin for prostate cancer (%)	1 (33)	0 (0)	0.27
Median time (months) of PSA surveillance (95% confidence interval)	23 (6-34)	22 (6-26)	0.59

Abbreviations: HGPIN, high-grade prostatic intraepithelial neoplasia; PSA, prostate-specific antigen

^{*} P value generated from Jonckheere-Terpstra test; other P values generated from Student's t-test for continuous variables and the Fischer's exact test or Mantel-Haenszel chi-square test for categorical variables.

^{**} No patients had positive lymph nodes for prostate cancer

Table 4

Peri-operative and clinical outcomes of the study population

Outcomes	Prostate capsule sparing cystectomy (n=20)	Nerve sparing cystectomy (n=20)	P Value
Peri-operative outcomes			
Estimated blood loss (mL), median (minimum, maximum)	400 (200, 1500)	575 (150, 2000)	0.19
Operative time (minutes), mean (SD)	395 (106)	411 (109)	0.65
Diversion type (%)			0.49
Neobladder	20 (100)	18 (90)	
Ileal conduit	0 (0)	2 (10)	
Clinical outcomes			
Hospital length of stay (days), median (minimum, maximum)	7 (5, 21)	8 (5, 21)	0.79
Duration of indwelling catheter (days), median (minimum, maximum)	21 (13, 47)	21 (12, 34)	0.96
30-day readmission rate (%)	0 (0)	3 (15)	0.23
90-day major complication rate [*] (%)	7 (35)	12 (60)	0.20

* Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher